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CHAPTER 42

Intravenous Admixtures

Salvatore J Turco, PharmD, FASHP

It has been estimated that 40% of all drugs administered in hospitals are given in the form of injections, and their use is increasing. Part of this increase in parenteral therapy is due to the wider use of intravenous fluids (IV fluids). In the last decade the use of IV fluids has doubled, increasing from 150 million units to 320 million units annually. Not only do IV fluids continue to serve as the means for fluid replacement, electrolyte-balance restoration, and supplementary nutrition, they also are playing major roles as vehicles for administration of other drug substances and in total parenteral nutrition (PN). Intravenous fluids are finding greater use as the means of administering other drugs because of convenience, the means of reducing the irritation potential of the drugs, and the desirability for continuous and intermittent drug therapy.

The techniques for providing PN parenterally have improved steadily in the last decade, and such use is increasing. The use of IV fluids for these purposes requires the compounding of specific intravenous admixtures (parenteral prescriptions) to meet the clinical needs of a given patient. However, the combination of drug substances in an IV fluid can promote parenteral incompatibilities and give rise to conditions not favorable for drug stability. A new area of specialization has been created for hospital pharmacists who can develop the expertise to prepare these solutions—recognizing their compatibility and stability problems and the potential for contamination—and participate in the administration of the solutions. The complex compounding of an order for PN requires knowledgeable personnel capable of making accurate calculations, compounding, and having aseptic technique. The parenteral prescription is becoming increasingly important in hospitals. Centralized admixture programs are now found in 90% of the nation's hospitals with 300 beds or more. Equipment available for administering IV fluids has become more sophisticated and has made possible increased accuracy of dosage and led to the development of new concepts and methods of nutrition and drug therapy.

Electronic mechanical equipment is now commonplace in hospitals. Its use, as well as its sophistication, continues to increase. Newly designed electronic pumps have been developed for hospital ambulatory use. Multichannel pumps have become available for multiple-drug infusion. Over 500,000 implantable infusion ports have been inserted into patients and 100,000 new patients receive these implantable ports each year to accomplish drug therapy. New methods of IV drug delivery systems have been introduced and are constantly evolving. The introduction of patient-controlled analgesia (PCA) is commonplace in hospitals. This technology allows the patient with pain to control the degree of analgesia.

The growth of PN in hospitals has been paralleled by home PN programs. Large numbers of patients conduct parenteral nutrition in the home environment, including those with infectious and neoplastic diseases. More-stringent and more-complete guidelines for the preparation of parenterals in hospitals by pharmacists have been published. These guidelines, promoting sophisticated methods of preparation by the pharmacist, have become recommendations. They are a testament to the importance of parenteral preparation in the institutional setting. Packaging of parenterals in the past 5 years also has undergone dramatic changes. Prefilled, premixed, prefrozen parenterals are now supplied by the manufacturers. Plastic minibags (ADD-Vantage, *Abbott*) have been introduced. Premixed liquids (eg, antibiotics, theophylline, heparin, lidocaine, dopamine) are available from parenteral manufacturers. Multiple-dose containers have been developed to accommodate new methods of preparation of parenterals by the pharmacist. The pharmaceutical industry has responded to the needs of pharmacists by addressing the packaging, labeling, and design requirements necessary to facilitate patient care. The parenteral drug industry continues its efforts to meet higher standards of quality and to ensure the availability of sterile and particulate-free products.

INTRAVENOUS FLUIDS

Large-volume injections intended to be administered by intravenous infusion commonly are called IV fluids and are included in the group of sterile products referred to as large-volume parenterals. These consist of single-dose injections having a volume of 100 mL or more and containing no added substances. Intravenous fluids are packaged in containers having a capacity of 100 to 1000 mL. Minitype infusion containers of 250-mL capacity are available with 50- and 100-mL partial fills for solution of drugs used in the *piggyback* technique (ie, the administration of a second solution through a Y-tube in the administration set of the first intravenous fluid, thus avoiding the need for another injection site). In addition to the IV fluids, this group also includes irrigation solutions and solutions for dialysis.

Intravenous fluids are sterile solutions of simple chemicals such as sugars, amino acids, or electrolytes—materials that easily can be carried by the circulatory system and assimilated. Prepared with Water for Injection USP, the solutions are pyrogen-free. Because of the large volumes administered intravenously, the absence of particulate matter assumes a significant role in view of possible biological hazards resulting from insoluble particles. Absence of particulate matter or clarity of IV fluids is as important at the time of administration following their manipulation in the hospital as it is at the time of manufacture of the injection.

Limits for particulate matter occurring in IV fluids or large-volume injections used for single-dose infusion are defined in

the USP. This represents the first regulatory attempt to define limits for particulate matter in parenterals. Limits also apply to multiple-dose injections, small-volume injections, or injections prepared by reconstitution from sterile solids. The USP defines particulate matter as extraneous, mobile, undissolved substances, other than gas bubbles, unintentionally present in parenteral solutions. The total numbers of particles having effective linear dimensions equal to or larger than 10 μm and larger than 25 μm are counted. The IV fluid meets the requirement of the test if it contains not more than 50 particles per mL that are equal to or larger than 10 μm and not more than 5 particles per mL that are equal to or larger than 25 μm in linear dimension.

Intravenous fluids commonly are used for a number of clinical conditions. These include:

Correction of disturbances in electrolyte balance.
Correction of disturbances in body fluids (fluid replacement).
The means of providing basic nutrition.
The basis for the practice of providing PN.
Vehicles for other drug substances.

In both of the latter two cases it has become common practice to add other drugs to certain IV fluids to meet the clinical needs of the patient. Using IV fluids as vehicles offers the advantages of convenience, the means of reducing the irritation potential of the drug, and a method for continuous drug therapy. However, the practice requires that careful consideration be given to the stability and compatibility of additives present in the IV fluids serving as the vehicle. This approach also demands strict adherence to aseptic techniques in adding the drugs as well as in the administration of the IV fluids. These procedures are discussed later in the chapter. The IV fluids commonly used for parenterals are shown in Table 42-1.

Many disease states result in electrolyte depletion and loss. Proper electrolyte concentration and balance in plasma and tissues are critical for proper body function. Electrolyte restoration and balance are achieved most rapidly through administration of IV fluids. Required electrolytes include sodium and chloride ions, which in normal saline more closely approximate the composition of the extracellular fluid than solutions of any other single salt; potassium, the principal intracellular cation of most body tissues and essential for the functioning of the nervous and muscular systems as well as the heart; magnesium, as a nutritional supplement especially in PN solutions; and phosphate ion, important in a variety of biochemical reactions. In addition to the number of standard electrolyte fluids shown in Table 42-1, a large number of combinations of electrolytes in varying concentrations are available commercially. Some of these electrolyte fluids also contain dextrose.

Dextrose Injection 5% (D5/W) is the most frequently used IV fluid, either for nutrition or for fluid replacement. It is slightly hypotonic and administered intravenously into a peripheral vein; 1 g of dextrose provides 3.4 cal, and 1 L of D5/W supplies 170 Kcal. The body uses dextrose at a rate of 0.5 g per kg of body weight per hour. More-rapid administration can result in glycosuria. Therefore, 1 L of D5/W requires 1 1/2 hr for assimilation. The pH range of D5/W can vary from 3.5 to 6.5. The wide range permitted is due to the free sugar acids

Table 42-1. Fluids Used Commonly for IV Use

INJECTION	CONCENTRATION (%)	PH	THERAPEUTIC USE
Alcohol			
with D5/W[a]	5	4.5	Sedative, analgesic, calories
with D5/W in NSS[b]	5		Sedative, analgesic, calories
Amino acid (synthetic)			Fluid and nutrient replenisher
Aminosyn II (*Abbott*)	3.5, 7, 8.5, 10, 15	5.25	
FreAmine III (*B.Braun*)	8.5, 10	6.6	
Travasol (*Baxter*)	3.5, 5.5, 8.5. 10	6.0	
Ammonium chloride	2.14	4.5–6.0	Metabolic alkalosis
Dextran 40			
in NSS	10	5	Priming fluid for plasma volume expander
in D5/W	10	4	Priming fluid for plasma volume expander
Dextran 70			
in NSS	6	5	Plasma volume expander
in D5/W	6	4	Plasma volume expander
Dextrose (glucose, D5/W)	2.5–50	3.5–6.5	Fluid and nutrient replenisher
Dextrose and sodium chloride	Varying concn of dextrose, 5–20, with varying concn of sodium chloride 0.22–0.9	3.5–6.5	Fluid, nutrient, and electrolyte replenisher
Lactated Ringer's (*Hartmann's*)		6.0–7.5	Systemic alkalizer; fluid and electrolyte replenisher
NaCl	0.6		
KCl	0.03		
$CaCl_2$	0.02		
Lactate	0.3		
Mannitol, also in combination with dextrose or sodium chloride	5 15 20	5.0–7.0	Osmotic diuresis
Multiple electrolyte solutions, varying combinations of electrolytes, dextrose,		5.5	Fluid and electrolyte replacement
Ringer's		5.0–7.5	Fluid and electrolyte replenisher
NaCl	0.86		
KCl	0.03		
$CaCl_2$	0.033		
Sodium bicarbonate	5	8	Metabolic acidosis
Sodium chloride	0.45, 0.9, 3, 5	4.5–7.0	Fluid and electrolyte replenisher
Sodium lactate	1/6 *M*	6.3–7.3	Fluid and electrolyte replenisher
Sterile water for injection		5.5	Diluent

[a] 5% Dextrose in water.
[b] Normal saline solution.

Table 42-2. IV Fluid Systems

SOURCE	CONTAINER	CHARACTERISTICS
Baxter	Glass	Vacuum Air tube
Baxter (*Viaflex*)	Plastic	Polyvinyl chloride Flexible Nonvented
B.Braun	Glass	Vacuum Air tube
B.Braun (*Excel*)	Plastic	Flexible
Abbott	Glass	Vacuum Air filter[a]
Abbott (*Lifecare*)	Plastic	Polyvinyl chloride Flexible Nonvented

[a] Part of administration set.

present and formed during the sterilization and storage of the injection. To avoid incompatibilities when other drug substances are added to Dextrose Injection, the possible low pH should be considered in using it as a vehicle. More-concentrated solutions of dextrose are available and provide increased caloric intake with less fluid volume. Being hypertonic, the more concentrated solutions may be irritating to peripheral veins. Highly concentrated solutions are administered in a larger central vein.

Intravenous fluids containing crystalline amino acids can provide biologically usable amino acids for protein synthesis (Chapter 106). Protein contributes to tissue growth, wound repair, and resistance to infection. The protein requirement for the normal adult is 1 g per kg per day; children and patients under stress require greater amounts. Attempts are made to maintain a positive nitrogen balance, indicating that the protein administered is being used properly and not broken down and eliminated through the urine as creatinine and urea, which are normal waste products. In a positive nitrogen balance patients are taking in more nitrogen than they are eliminating. In a negative nitrogen balance there is more nitrogen being eliminated through the urine regularly than is being administered intravenously. This means that tissues are continuing to be torn down, and repair is not necessarily taking place. Amino Acid Injection can afford the total body requirements for proteins by the procedure known as PN (discussed below) or be used for supplemental nutrition by peripheral administration. In addition to the amino acids, these nutritional injections also may contain dextrose, electrolytes, vitamins, and insulin. Fat emulsion (Intralipid, *Baxter*; Liposyn II, *Abbott*) sometimes is used concurrently but usually administered at Y-site. However, new systems such as three-in-one packaging permit mixing of amino acids, carbohydrates, and fat in one container for PN.

Packaging Systems

Containers for intravenous fluids must be designed to maintain solution sterility, clarity (freedom from particulate matter), and nonpyrogenicity from the time of preparation, through storage, and during clinical administration. Container closures must be designed to facilitate insertion of administration sets through which the injections are administered at a regulated flow-rate into suitable veins. IV fluids are available in glass and plastic containers; the latter are made from a flexible plastic material. IV fluids are supplied in 1000-mL, 500-mL and 250-mL sizes in addition to 250-mL capacity containers packaged with 50 or 100 mL of D5/W or sodium chloride injection 0.9% for piggyback use in addition to 0.45% sodium chloride and 2.5% dextrose injections. IV fluids in glass containers are packaged under vacuum, which must be dissipated prior to use. For fluid to leave the IV glass container and flow through the administration set, some mechanism is necessary to permit air to enter the container. Current flexible plastic systems do not require air introduction to function. Atmospheric pressure pressing on the container forces the fluid to flow.

All glass and plastic containers are single-dose and should be discarded after opening even if not used. Intravenous fluids are packaged with approximately 3% excess fill to allow for removal of air from the administration set and permit the labeled volume to be delivered from the container. The containers are graduated at 20-mL increments on scales that permit the volume in a container to be determined from either an upright or inverted position. Glass containers have aluminum and plastic bands for hanging, while plastic containers have eyelet openings or plastic straps for attachment to IV poles.

Fluids for IV use are available from three sources (*Abbott, Baxter,* and *B.Braun*); all provide both glass and plastic containers. The glass-container systems of *Baxter* and *B.Braun* are similar. The characteristics of current packaging systems are summarized in Table 42-2.

Administration Sets

Administration sets used to deliver fluids intravenously are sterile, pyrogen-free, and disposable. Although these sets are supplied by different manufacturers, each for its own system, they have certain basic components. These usually include a plastic spike to pierce the rubber closure or plastic seal on the IV container, a drip (sight) chamber to trap air and permit adjustment of flow rate, and a length (150 to 450 cm) of polyvinyl chloride (PVC) tubing terminating in a gum-rubber injection port. Non–PVC sets are available for special uses. At the tip of the port is a rigid needle or catheter adapter. An adjustable clamp (screw or roller type) on the tubing pinches the tubing to regulate flow. Since the Y-site port is self-sealing, additional medication can be added to the IV system at these ports of entry. Glass containers that have no air tubes require air-inlet filters designed as part of the administration set (*Abbott*). See Figures 42-1 to 42-6.

Administration Procedures

In the administration of IV fluids, the primary IV container provides for fluid replacement, electrolyte replenishment, drug therapy, or nutrition; the fluid can be infused usually over a 4- to 12-hr period. In some cases an IV fluid is infused slowly for the purpose of keeping the vein open (KVO). This will allow additional drugs to be administered when required. The primary IV fluid also can serve as a vehicle for other drugs to be administered, thus becoming an intravenous admixture (IV drip), and

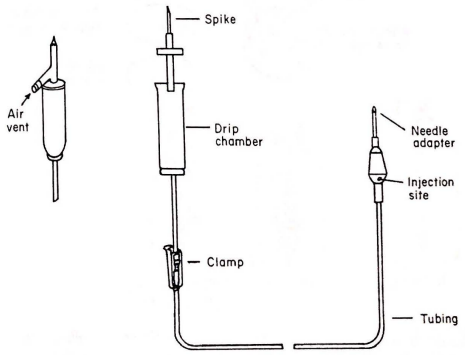

Figure 42-1. Parts of basic administration sets.

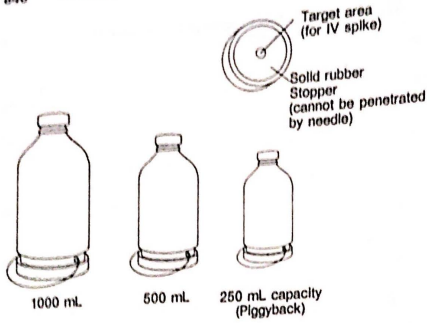

Figure 42-2. Abbott IV glass container. The air venting is provided through the air filter located in the spike of the administration set. See Figure 42-1.

results in continuous blood levels of added drugs once the steady state has been reached.

Incinerated PVC products produce hydrogen chloride gas as a toxic pollutant. Diethylhexylphthalate (DEHP), a component of PVC containers, may leach into the soil in landfills. A number of drugs adsorb on PVC containers, notably nitroglycerin. Some drugs (fat emulsions, blood, Paclitaxel) are known to leach DEHP.

The Excel container is claimed to eliminate or minimize these problems. The plastic film contains no plasticizers and exhibits no leachability. The solution-contact layer of the container is composed of a rubberized copolymer of ethylene and propylene, which is claimed to be clear, nontoxic, and biologically inert. The container is available in 250-mL, 500-mL, and 1-L sizes. Smaller sizes are available in 25, 50, and 100 mL known as PAB containers.

In preparing an IV fluid for administration, the following procedure is used.

The spike adapter of the administration set is inserted into the stopper or seal of the IV container.

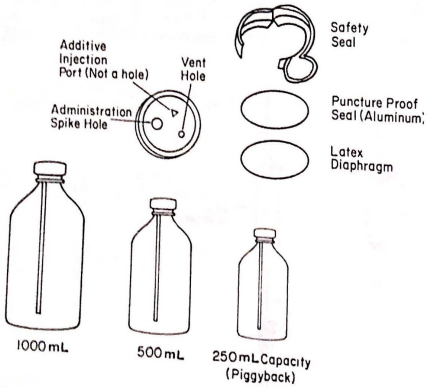

Figure 42-3. B.Braun glass containers. The plastic air tube allows the air to enter the bottle as the fluid is infused into the patient. The spike of the administration set is not vented. See Figure 42-1.

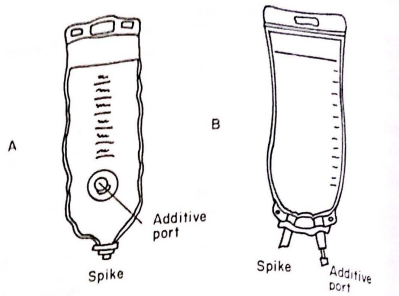

Figure 42-4. *A,* Abbott (Lifecare) polyvinyl chloride flexible container. *B,* Baxter (Viaflex) polyvinyl chloride flexible container. These containers take nonvented administration sets. See Figure 42-1.

The IV fluid is hung on a stand at bedside, and air is purged from the administration set by opening the clamp until fluid comes out of needle. The tubing is then clamped off.

The venipuncture is made by a member of the IV team, floor nurse, or physician.

The infusion rate is adjusted by slowly opening and closing the clamp until the desired drop rate, viewed in the drip chamber, is obtained. The usual running time is 4 to 8 hr (usually 125 mL is delivered in 1 hr). Drugs such as heparin, insulin, lidocaine, or dopamine may be present in the IV drip. When potent drugs are present, the flow rates will vary, depending on the clinical condition of the patient. Sets are calculated to deliver 10, 15, 20, 50, or 60 drops per mL, depending on the manufacturer. Critical drugs are usually administered by electronic pumps.

Intermittent administration of an antibiotic and other drugs can be achieved by any of three methods:

1. Direct IV injection (IV bolus or push)
2. Addition of the drug to a predetermined volume of fluid in a volume-control device
3. Use of a second container (minibottle, minibag) with an already hanging IV fluid (piggybacking)

DIRECT INTRAVENOUS INJECTION—Small volumes (1 to 50 mL) of drugs are injected into the vein over a short period of time (1 to 5 min). The injection also can be made through a resealable Y injection site of an already hanging IV fluid. This method is suitable for a limited number of drugs but too hazardous for most drugs.

VOLUME-CONTROL METHOD—Volume-control sets provide a means for intermittent infusion of drug solutions in precise quantities at controlled rates of flow. These units consist of calibrated, plastic, fluid chambers placed in a direct line under an established primary IV container or more often attached to an independent fluid supply. In either case, the drug to be administered is first reconstituted if it is a sterile solid and injected into the gum-rubber injection port of the volume-control unit. It is then further diluted to 50 to 150 mL with the primary fluid or the separate fluid reservoir. Administration of the total drug-containing solution requires 30 to 60 min and produces a peak concentration in the blood followed by a valley if the dosage is discontinued.

To set up an intermittent IV infusion with a volume-control set, the spike of the volume-control set is inserted into the primary IV fluid or a separate fluid container using aseptic technique. See Figure 42-6.

Air is purged from tubing of the volume-control set by opening the clamps until fluid comes through.

The clamp is opened above the calibrated chamber, and it is filled with 25 to 50 mL fluid from the primary IV container or separate fluid container.

The clamp is closed above the chamber.

The medication is injected through the gum-rubber port of the volume-control unit.

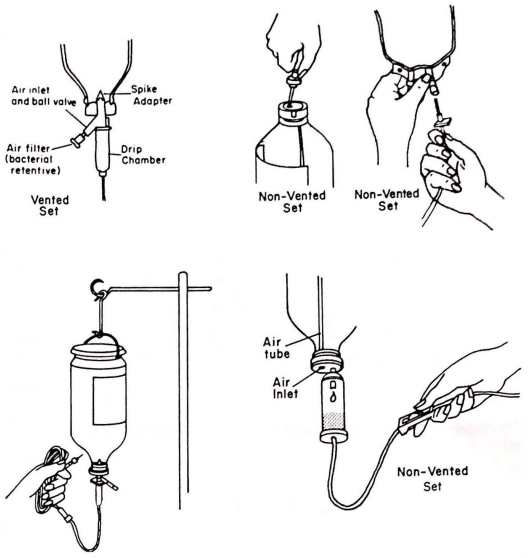

Figure 42-5. Setting up a primary IV fluid for administration.

The clamp above the chamber is opened to complete the dilution to the desired volume (50 to 150 mL), then closed.
Flow commences when the clamp below the volume-control unit is opened.

PIGGYBACK METHOD—The piggyback method (Fig 42-7) refers to the intermittent IV drip of a second admixture drug, through the venipuncture site of an established primary IV system. With this setup the drug can be thought of as entering the vein on *top* of the primary IV fluid, hence the designation *piggyback*. The piggyback technique not only eliminates the need for another venipuncture, but also achieves drug dilution and peak blood levels within a relatively short timespan, usually 30 to 60 min. Drug dilution helps to reduce irritation, and early high serum levels are an important consideration in serious infection requiring aggressive drug therapy. These advantages have popularized the piggyback method of IV therapy, especially for the intermittent administration of antibiotics. In using the piggyback technique, the secondary unit is purged of air, and its needle or blunt cannula inserted into a Y-injection site of the primary set or into the injection site at the end of the primary set.

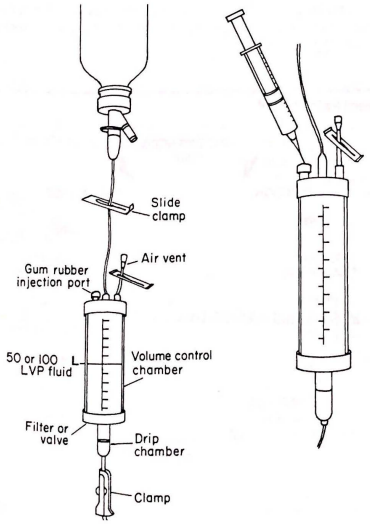

Figure 42-6. Volume control unit for intermittent administration.

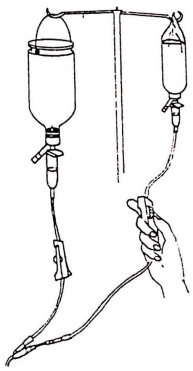

Figure 42-7. Piggyback administration setup.

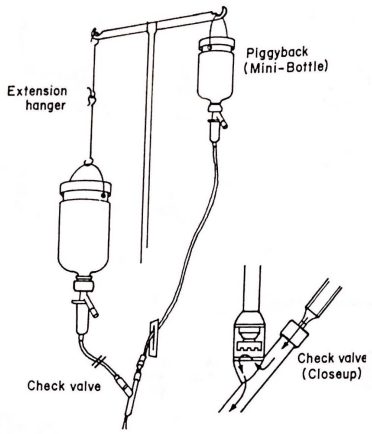

Figure 42-8. Piggyback administration setup with check valve in primary set.

The piggyback infusion is then started. Once it is completed, the primary fluid infusion will be restarted. See Figure 42-7.

Primary IV administration sets are available that have a built-in check valve for use in piggyback administration. When the piggyback is connected to one of these sets and started, the check valve automatically closes off the primary infusion. When the piggyback runs out, the check valve automatically opens, thereby restarting the primary infusion. The check valve works because of pressure differences. To achieve this difference, the primary container is hung lower than the secondary bottle by means of an extension hanger. See Figure 42-8.

Manufacturers have introduced minibottles and minibags prefilled with various antibiotic products; each container is provided with a plastic hanger for direct suspension from an IV pole as the piggyback solution is administered through the resealable gum-rubber injection site or Y-type facility of an existing IV system. Reconstitution of piggyback units requires only the addition of a small volume of compatible diluent. Since reconstitution and administration proceed from the same bottle, no drug transfer is involved, so transfer syringes and additional IV containers are not necessary. Prefilled drug containers offer significant advantages to hospitals. Time-saving, less potential for error and contamination, and convenience are outstanding qualities of this type of packaging. The need exists in hospitals for these types of innovative packaging to help alleviate the critical nursing shortage and reduce the error potential. It is a significant event that drug manufacturers and intravenous fluid manufacturers have combined efforts to achieve optimal packaging for hospital use.

Partial-fill containers available for piggybacking are 250-mL capacity infusion bottles or bags underfilled with 50 or 100 mL D5/W or normal saline. The drug to be administered first is reconstituted in its original parenteral vial and then added by needle and syringe to the partial-fill container. The needle of the piggyback delivery system is inserted into the Y-site or gum-rubber injection port of a hanging primary infusion set. Flow of the primary intravenous fluid is stopped while the drug solution in the partial-fill container is administered (30 to 60 min). After the drug solution has been infused totally, the primary fluid flow is reestablished. When the next dose of drug is required, the piggyback procedure is repeated, replacing the prefilled partial-fill container.

MECHANICAL-ELECTRONIC INFUSION DEVICES—Gravity IV administration systems are affected by many variables that tend to alter the accuracy of the system. These include variations in the size of the drip-chamber orifice, the viscosity of the solution being administered, plastic cold flow, clamp slippage, final filters, variations in the patient's blood pressure and body movements, clot formation, pressure changes in IV containers' rate of flow, temperature of the IV fluid, changes in the needle, and other factors such as kinked tubing, extravasation, and changes in the height of the IV container. Flow in traditional gravity IV systems is controlled by manual clamps (either screw or roller clamps), which can provide considerable discrepancies in volume delivery. These factors have promoted the development and use of mechanical-electronic infusion devices to control more accurately the administration of IV fluids. This group of devices includes infusion controllers and infusion pumps.

Infusion controllers count drops electronically or extrude volumes of fluid mechanically and electronically. Having no moving components, controllers are less complex than pumps, are usually less expensive, and have fewer maintenance problems. Infusion controllers are gravity-type systems, but the control is regulated automatically rather than manually. In addition to increasing the accuracy of delivery, electronic equipment may be able to detect infiltration of air, empty containers, and excess or deficient flow. Controllers are used less frequently in favor of pumps.

Infusion pumps do not depend on gravity to provide the pressure required to infuse the drug. Pressure is provided by an electric pump that propels a syringe, a peristaltic or roller device, or a cassette. Most pumps are volumetric in that the delivery is measured in milliliters rather than drops.

The quality of patient care has improved with the use of infusion devices. Flow rates can be maintained; therefore parenteral and enteral nutrition can be conducted safely. In addition, accurate drug therapy can be accomplished with adults and children, and *runaways* of IV fluid administration can be eliminated.

PATIENT-CONTROLLED ANALGESIA (PCA)—Usually and traditionally the acute or chronic pain experienced by patients in selected diseases is treated initially by oral narcotics and analgesics. However, many clinical situations preclude oral administration. Typically, the unsatisfied pain from disease has been treated by parenteral analgesics given by the IM or SC route.

This medication cycle from patient complaint to pain relief often can be lengthy. Frequently, the dose administered may be too large or too small, resulting in either sedation or poor pain relief. See Figure 42-9.

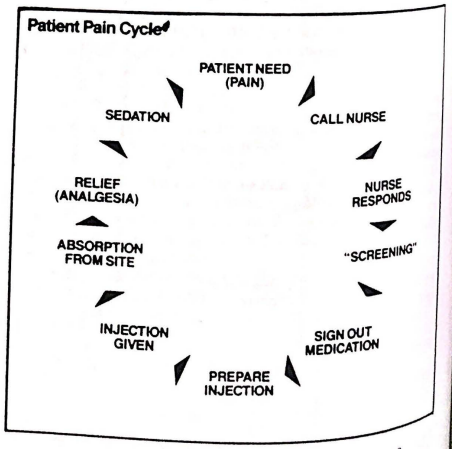

Figure 42-9. Patient pain cycle—sequence of events.[3]

Parenteral drugs given intravenously offer rapid distribution in the body and fast onset of action. The drug undergoes no biotransformation or inactivation and, therefore, allows more precise dose management.

PCA is a system for delivery of IV or SC narcotics by direct patient intervention. This therapy uses a mechanical, electronic, infusion-control device that permits self-administration of analgesics in proportion to the degree of relief desired.

A number of these devices have been developed and are undergoing development at *Bard, Abbott, Deltec, Baxter,* and *Becton Dickinson.* The early devices allowed for patient- triggered IV doses, and later refinement in the microprocessors allowed tailoring of infusions so that additional bolus doses could be given to a baseline infusion. Additional developments have led to ambulatory PCA devices that are small enough to be worn on a belt. An additional design being used is a balloon-powered disposable device (*Baxter*) that operates mechanically from an inflated balloon.

In its simplest terms, PCA allows a patient to initiate an IV infusion of a prescribed narcotic analgesic and maintain a self-regulated small amount of incremental doses needed for controlling a variety of pain-associated medical problems.

The success and popularity of PCA is based upon the inadequacy of conventional IM and IV dosing, such as variables that affect absorption and distribution[1] such as conventional nursing practices, inherent procedural delays in securing medication, and the ultimate administration to the patient.[2] The perception and sensation of pain in any one patient depends upon individual levels of endorphins and other biochemicals in cerebrospinal fluid.[3]

The last several years have seen the increasing use of infusion devices for epidural or intrathecal administration.

PCA eliminates the peak and valley effects of traditional drug therapy (Fig 42-10). Epidural or intrathecal therapy of PCA allows a longer duration of drug action. Kwan[4] reviewed the use of infusion devices for epidural or intrathecal administration.

FINAL-FILTER DEVICES—Particulate matter in IV fluids and IV admixtures can originate from many sources. It can result from the packaging components of the IV fluid, from admixture incompatibilities, from manipulation in preparing the admixture, and even from the administration set itself. Concern about particulate matter led to the design of final-filter devices for attaching to the end of the tubing of the administration set. They afford a final filtration of the IV fluid before it passes through the needle into the vein. The device consists of a plastic chamber containing a membrane or stainless steel filter

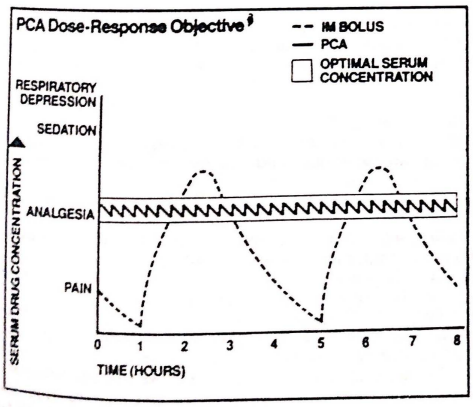

Figure 42-10. Characteristic pattern comparison of IM bolus serum concentration versus PCA.[3]

with porosities varying from 5 to 0.22 μm. Air lock can be a problem with membrane filters. When wet, membranes with porosities of 0.22 μm and 0.45 μm are impervious to air at normal pressures, and air in the system causes blockage. To prevent this, the filter housing must be purged completely of air prior to use. Newer designs have air eliminators. Using final-filter devices increases medication cost but reduces the biological hazards associated with particulate matter.

Although considerable information is available concerning the clinical use of membrane filters in entrapping particulate matter and microorganisms, little information exists describing drug absorption by the filter. Literature on a limited number of drugs and filter materials indicates that drugs administered in low doses might present a problem with drug bonding to the filter.[5] Solutions containing minute dosages of drugs, 5 mg or less, should not be filtered until sufficient data are available to confirm insignificant absorption. Drugs not recommended to be filtered include all parenteral suspensions, blood and blood products, amphotericin B, digitoxin, insulin, intravenous fat emulsions, mithramycin, nitroglycerin, and vincristine.

Blood is filtered by utilizing blood filters of larger porosity (210 microns).

2 in 1 TPN solutions usually require a 0.22 micron filter.

3 in 1 TPN solutions usually require a 1.2 micron filter.

IV DELIVERY SYSTEMS—*Frozen Premixes*—Baxter provides delivery to hospitals of frozen drug products packaged in PVC containers. These are stored in a freezer in the hospital's pharmacy, thawed, and used when needed. See Figure 42-11*A*.

Abbott/ADD-Vantage System—Introduced in 1985, the *Abbott* ADD-Vantage system (Fig 42-11*B*) has two parts: a plastic IV bag (Abbott) that is filled with solution and a separate glass vial of powder or liquid drug sold by a pharmaceutical manufacturer. The vial is encased in a plastic cover that is removed prior to use. The user locks the vial holding the drug into a chamber at the top of the plastic bag and mixes the drug and solution by externally removing the stopper on the vial which allows drugs to fall into the diluent.

Nutrimix—A dual-compartment container is available from Abbott that allows long-term packaging of amino acids and dextrose mixtures.

Mini-Infuser Pumps for Intermittent IV Drug Delivery—A novel concept in intermittent drug delivery, introduced several years ago, was the Bard-Harvard Mini-Infuser System. This instrument was designed for the administration of antibiotics and other medications delivered intermittently in 40 min or less. This battery-generated, lightweight instrument uses standard disposable syringes and microbore disposable extension sets. Different models are available depending on the volume to be delivered. This instrument provides accuracy, constant flow, convenience, and safety for intermittent drug delivery. See Figure 42-11*C*.

Introduced and designed for intermittent IV drug delivery, Becton Dickinson's 360 Infusor allows drug delivery intermittently over 60 min or less in a volume dilution of up to 60 mL.

INTERNAL METHODS USED TO ACHIEVE INTRAVASCULAR ACCESS—*Implantable Ports* (Infuse-A-Port, *Infusaid;* Port-A-Cath, *Pharmacia*)—Broviac and Hickman catheters have been used to achieve long-term venous access in a variety of diseases. Although these catheters are widely used, they are associated with some morbidity, which includes fracture of catheters, entrance-site infection, and catheter sepsis. Implantable catheters have been developed to overcome catheter complications and are designed to permit repeated access to the infusion site. The catheters consist of implantable-grade silicone tubing connected to a stainless steel port with a self-sealing septum that allows needle access. The delivery catheter can be placed in a vein, cavity, artery, or the central nervous system (CNS). The system is accessed with a Huber-point needle through the skin into the self-sealing silicone plug positioned in the center of the portal.

The specialized Huber-point needle is designed with an angle bevel that reduces coring and permits easy entry. These

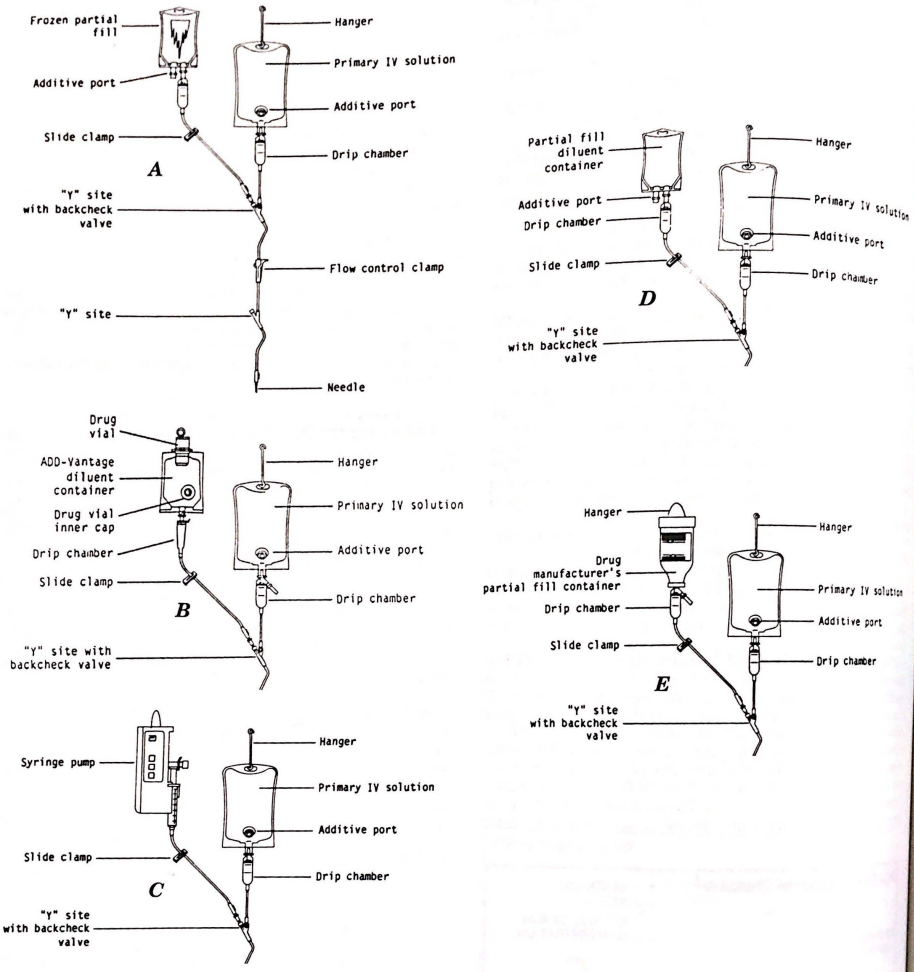

Figure 42-11. Various IV delivery systems. *A,* Frozen partial fill; *B,* ADD-Vantage; *C,* syringe pump; *D,* partial-fill diluent container; *E,* drug manufacturer's partial-fill piggyback (DMP) (courtesy, Abbott). The flow control clamp, "Y" site, needle, and associated tubing for *B* through *E,* are the same as in *A.* (Fig 42-11 is continued on the next page.)

implantable ports can be used for the injection of IV fluids, total parenteral nutrition, chemotherapy, antibiotics, and other drugs.

Some advantages of implantable devices include

The need for a long-term access site to venous, arterial, and spinal systems
An increased dependence on non-hospital treatment of chronic disease states
The direct infusion in a target organ or tumor
A decrease in infection rates that are seen with percutaneous catheters or repeated spinal taps
A greater mobility for the patient (a return to normal function)

Implantable Pump (Infusaid)—The Infusaid Implantable Pump was approved for selected drug administration. This pump is the size of a hockey puck and weighs approximately 1/2 oz. The construction is titanium, stainless steel, and polypropylene. The injection port is constructed of silicone rubber and has a usable life of at least 2000 punctures. Under normal use this device lasts more than 8 years.

The internal power supply uses Freon in equilibrium between the gaseous and liquid states and is recharged with each refilling process, thus supplying a power supply for as long as the pump is needed. As the pump is refilled, it compresses the gas back into the liquid state, allowing a fresh supply of energy

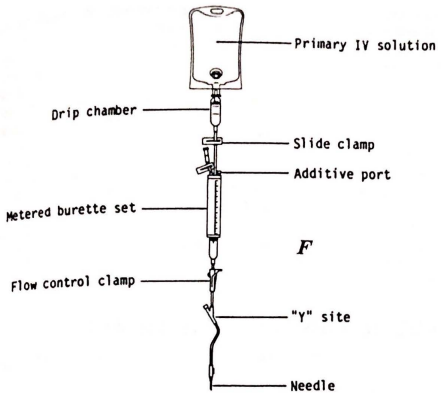

Figure 42-11 (continued). *F,* burette set (courtesy, Abbott).

for the next cycle. The capacity of this pump is 50 mL, which can be administered over a 14-day period. The pump accuracy is stated as over 3%. The cost of one model is approximately $4000.00, not including the surgical implant procedure. The 14-day cycle cannot be altered to any degree.

Model 400 Implantable Drug Delivery System (Infusaid) is designed for long-term therapy in the ambulatory patient. The Model 400 with a 47-mL usable drug volume delivers a precise, continuous flow to a selected organ or site via a soft, nontraumatic, nonthrombogenic, silicone rubber catheter. The Model 400 also features an auxiliary Sideport septum, completely bypassing the pumping mechanism, for delivery of direct bolus injections to the target site. Thus the clinician can easily supplement the continuous infusion with additional drugs, objectively assess the disease state, or monitor catheter location and drug perfusion with the use of radiolabeled microspheres.

INTRAVENOUS ADMIXTURES

When one or more sterile products are added to an IV fluid for administration, the resulting combination is known as an IV admixture. To maintain the characteristics of sterile products, namely, sterility and freedom from particulate matter and pyrogens, it is imperative that they be manipulated in a suitable environment by use of aseptic techniques.

ENVIRONMENT—Proper conditions for aseptic handling can be provided by laminar-flow hoods (see Chapters 40 and 41). Within a laminar-flow hood, air filtered through a HEPA (high-efficiency particulate air) filter moves in a parallel flow configuration at a velocity of 90 fpm. HEPA filters remove 99.97% of all particles larger than 0.3 μm. Since microbial contaminants present in air usually are found on other particulates, removal of the latter results in a flow of air free of both microbial contaminants and particulate matter. The movement of the filtered air in a laminar-flow configuration at a velocity of 90 fpm can maintain the area free of contamination. The flow of air may be in either a horizontal or vertical pattern. In the former case the HEPA filter is located at the back of the hood and the air flows to the front. In vertical flow the air passes through the HEPA filter located in the top of the cabinet and is exhausted through a grated area around the working surface of the hood. Regardless of the type of laminar air flow, the hood must be operated and maintained properly to achieve a satisfactory environment for the preparation of parenteral admixtures.

The hood is situated best in a clean area in which there is little traffic flow past the front of the hood. The inside of the hood is wiped down thoroughly with a suitable disinfectant and allowed to run for at least 30 min before starting manipulations. It is important to remember that the laminar-flow hood is not a means of sterilization. It only maintains an area free of microbial contaminants and particulate matter when it has been prepared, maintained, and used properly by operators with proper aseptic techniques.

Before working in a laminar-flow hood, operators wash their hands thoroughly and scrub them with a suitable disinfectant. Some institutions may require gowning and use of sterile gloves. Sterile gloves can be an asset, but there is always the problem that they can give the operator a false sense of security. Gloved hands can become contaminated as easily as ungloved hands. Additives and IV fluids to be used in the preparation of the admixture, along with suitable syringes, are lined up in the hood in the order they are to be used. The containers must be clean and dust-free. They are inspected for clarity and freedom from cracks. Operators are encouraged to use a lighting device for inspecting IV fluids for particulate matter and cracks. The lighting device should permit the container to be viewed against both a light and a dark background during inspection. If the IV fluid is packaged in plastic containers, pressure is applied to ensure that they are sealed properly and do not leak. Some laboratories disinfect the containers prior to placing them in the hood.

In working within the hood the operators work in the center of the hood, with the space between the point of operation and the filter unobstructed. If the flow of air is blocked, the validity of the laminar flow is destroyed. Articles are arranged within the hood in a manner to prevent clean air from washing over dirty objects and contaminating other objects that must remain sterile. The working area must be at least 6 inches from the front edge of the hood. As the operators stand in front of the hood, their bodies act as a barrier to the laminar air flow causing it to pass around them and create backflow patterns that can carry room air into the front of the hood.

Laminar-flow hoods must be maintained and evaluated periodically to ensure that they are functioning properly. The velocity of air flow can be determined routinely using a velometer. A decrease in the air flow usually indicates a clogged HEPA filter. Some laminar-flow hoods are equipped with pressure gauges indicating pressure in the plenum behind the filter; in these hoods pressure increase also can indicate a clogged filter. Settling plates can be exposed within the hood for given periods of time to determine the presence of microbial contaminants.

The best way to determine the proper functioning of a HEPA filter is to use the dioctylphthalate (DOP) test using the vapor at room temperature. DOP vapor (particles of ;0.3 μm) is allowed to be taken up by the hood through its intake filter. If the HEPA filter is intact and properly installed, no DOP can be detected in the filtered air stream by use of a smoke photometer. Certification services are available through commercial laboratories; the HEPA filters within laminar-flow hoods should be evaluated every 6 months.

ADDITIVES—The additives are injections packaged in ampuls or vials, or sterile solids; the latter are reconstituted with a suitable diluent before addition to the IV fluid. A fresh, sterile, disposable syringe is used for each additive. Before removing a measured volume from an ampul, the container is wiped with a disinfectant solution. If the ampul is scored, the top can be snapped off; if not scored, an ampul file must be used. A sterile syringe is removed from its protective wrapping. The syringe needle with its cover is separated from the syringe aseptically and may be replaced with a sterile aspirating needle. Aspirating needles usually are made from clear plastic and contain a stainless steel or nylon filter with a porosity of 5 μm. The filter will remove glass particles and other particulates from the injection as it is drawn up from the ampul into the syringe. The aspirating needle is replaced with the regular needle. The exact volume is calibrated, and the injection is ready to be added to

the IV fluid (see Fig 42-12). In the case of additives packaged in multiple-dose vials, the protective cover is removed and the exposed target area of the rubber closure disinfected. A volume of air, equal to the volume of solution to be removed, is drawn up into the syringe and injected into the air space above the injection within the vial. This facilitates withdrawal of the injection. The solution is drawn into the syringe, the exact dose is measured, and the injection is ready to be added to the IV fluid.

Certain injections are light-sensitive and protected against photolysis by the container packaging. The manufacturer may use amber glass, individual container wrapping, or an amber plastic cover. Many hospital pharmacists use aluminum foil as a protective wrap for light-sensitive drugs during their administration.

In the case of drug substances having poor stability in aqueous solution, the drug is packaged as a sterile solid, either dry-filled or lyophilized. The diluent recommended on the labeling is used to reconstitute the powder; the proper quantity of solution then is removed for addition to the IV fluid. To increase the efficiency of IV admixture programs, a limited number of hospital pharmacists have found it convenient to freeze reconstituted drugs, particularly antibiotics. The stability of reconstituted drugs is somewhat limited. In some cases stability is limited to only a few hours; in many cases, however, reconstituted solutions can be frozen and thawed at the time of use. In the frozen form the stability of the antibiotic solution can be increased. In a number of instances the stability in the frozen form is known and supplied by the manufacturer. Reports have been published on the frozen stability of certain drugs. However, it is unwise to freeze drug solutions without adequate stability studies for guidance. In those cases where published information is available, close adherence must be observed as to freezing temperature, storage conditions, and packaging.

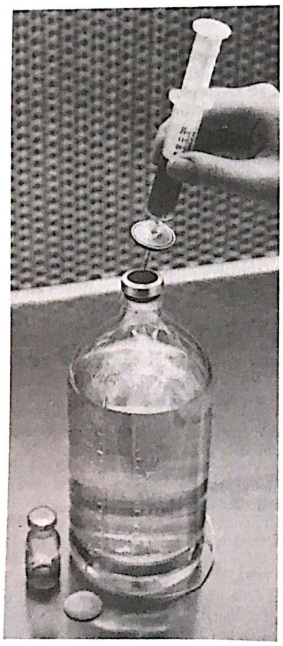

Figure 42-12. Placing an additive into an IV fluid with filtration through a membrane filter (courtesy, Millipore)

There is an increasing awareness of the potential hazard to pharmacists handling antineoplastic drugs.[6] Although the evidence is not conclusive, it appears that measures should be taken to minimize unnecessary exposure.[7,8] These precautions include the use of vertical laminar-flow hoods and biological safety cabinets for the preparation and reconstitution of these agents, the wearing of gloves and masks by the personnel, special labeling of the containers to ensure their proper handling and disposal, and periodic blood studies of personnel involved in preparing admixtures of antineoplastic agents.

The procedure for placing an additive in an IV fluid will vary depending on the type of IV fluid packaging system being used by the hospital. The packaging systems are described in Table 42-2.

Abbott Glass Containers (Fig 42-2)

1. Remove the aluminum tear seal exposing the solid-rubber closure with a target circle in the center.
2. Wipe the closure with suitable disinfectant.
3. Insert the needle of the additive syringe through the target area. The vacuum within the bottle draws in the solution.
4. Gently shake the bottle after each addition, to mix thoroughly.
5. When completed, cover the closure with a plastic protective cap if it is not to be used immediately.

Baxter and McGaw Rigid Glass Containers (Fig 42-3)

1. Remove the aluminum tear seal and the aluminum disk covering the latex diaphragm.
2. Upon exposing the latex diaphragm, note that the latex cover is drawn in over the openings in the rubber closure.
3. The larger of the two holes receives the administration set, the other is the air vent. The triangular indentation can serve as the site for injecting the additives as well as the opening for the administration set.
4. Wipe the diaphragm with a suitable disinfectant and pierce the latex cover to place additive into bottle. The vacuum within the bottle will draw additive from the syringe. Do not remove the diaphragm or the vacuum will dissipate. It will be removed at the time of administration prior to the insertion of the administration set.
5. Gently shake the bottle after each additive.
6. When completed, cover the bottle with a plastic additive cap if the administration set is not to be inserted immediately.

Baxter and Abbott Plastic Container (Fig 42-4)

1. Remove the additive port protective sleeve and swab the injection port plug with a suitable disinfectant.
2. Additives are placed in container by piercing the additive port, mix thoroughly.
3. After each addition, milk the container to ensure adequate mixing.
4. Containers do not contain a vacuum, but vacuum chambers are available for use in conjunction with the flexible plastic container.
5. Protective additive caps are available if the administration set is not inserted immediately.

PHARMACY BULK PACKAGE—The manufactured bulk package is a sterile container for parenteral use that contains many single doses. These containers are intended for use in admixture programs in which large numbers of doses are prepared. It is designed so that the rubber closure is penetrated only once. It is used in laminar-flow hoods. Pharmacy bulk packages are exempt from the USP requirement that multiple-dose containers have a volume not greater than 30 mL. They also have an exemption in that they are not required to have a bacteriostatic agent. Pharmacy bulk packages have special labeling and storage requirements.